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A reappraisal of non-specific genital infection with reference to the work of the late Dr E Weston Hurst

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SUMMARY It is easy to overlook work that is before its time, especially if it has been done in the recent past. In his animal experimental work with *Chlamydia* spp, the late Dr E Weston Hurst found that although he was able to effect a clinical cure in his intraperitoneally infected mice, he was unable to eradicate their infections. As his work appears to have relevance to today's growing problems concerning genital infections associated with chlamydiae, it should not fall into obscurity.

Introduction

It was Dunlop *et al* who in 1964 first reported growing *Chlamydia trachomatis* from a man with non-specific urethritis (NSU).[1] Such major research successes tend to make us overlook other painstakingly acquired information. This historical comment aims to prevent such a fate befalling the work of Dr Weston Hurst who died in 1971 and for whom no obituary appeared in either the British Medical Journal or the Lancet.

Weston Hurst directed the virology division of Imperial Chemical Industries (ICI) in Manchester and, in his later years, in the company's new laboratories at Alderley Edge in Cheshire. He had many fine qualities but is best remembered by colleagues and assistants for his thoroughness in organising and pursuing his researches. It is said that each organism he studied was given a colour code which was used in all aspects of research from bottle tops to protective clothing. The relevant observations he made spanned the years 1948-62.

For some time after the second world war the organisms now known as chlamydiae were described as large viruses, for which ICI was seeking new antiviral agents. Weston Hurst, therefore, conducted many laboratory animal experiments with large viruses, particularly those responsible for lymphogranuloma venereum (LGV), psittacosis, and (later) trachoma.

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Historical perspective

For many years NSU was thought to be caused by a sexually transmitted large virus. This view was based on the occasional finding of inclusion bodies in smears from patients with NSU,[2] the epidemiology of the condition, and its response to antimicrobials, especially the tetracyclines. Weston Hurst treated his infected animals with a variety of antimicrobials which he ranked according to their antiviral activity as determined by clinical cure.[3] His findings corresponded closely with those found when a similar group of drugs was used to treat NSU. It was agreed that tetracyclines were the most effective, but they were also associated with the highest recurrence rates[4] and Fowler thought they were only marginally better than placebo.[5]

In the 'fifties the length of tetracycline courses for NSU varied from four to seven days and seven day courses continue to be recommended[6]; a widening variety of tetracycline preparations have been subjected to comparative trials.[7-9] Recurrence rates of at least 10-20% after one to three months' follow up are regularly reported and it is widely recognised that the longer the follow up the greater the recurrence rate.[9 10] Like Bhattacharyya and Morton who compared seven and 21 day courses of tetracyclines,[11] Evans believed that most early recurrences were relapses and only a small proportion, which increased with time, were caused by reinfection.[9] Relapses in lymphogranuloma venereum and in trachoma are common and unquestioned. In the latter, clinical relapse is rarely associated with finding the causative organism. Yields of *C trachomatis* in recurrent NSU are consistently lower than those associated with

initial attacks. Handsfield *et al* were able to demonstrate the organism only in patients with recurrence of NSU more than six weeks after treatment.[12] Evans noted that 85% of his patients with early recurrence (within a month of treatment) denied sexual intercourse within that time.[8] In the laboratory Weston Hurst also noted recurrence in his intraperitoneally infected animals when they were apparently cured and free from the possibility of reinfection.[3 13]

The view that recurrence of NSU is often due to some endogenous factor is reinforced by observations suggesting that recurrence rates are not influenced by treating the sexual partners of men with the condition.[4 8 9 14] Observations of relapse after more prolonged courses of treatment[11] were also supported by Weston Hurst, who encountered recurrences even after courses of tetracyclines lasting 35-50 days.[15]

Strains D-K of *C trachomatis* have been identified in up to 60% of patients with NSU and in 30-60% of their sexual partners. Other organisms, particularly *Ureaplasma urealyticum,* have been suggested as being responsible but undetected *C trachomatis* should now be thought an equally likely cause. *C trachomatis* is also implicated in the increasingly recognised complicated forms of non-specific genital infection (NSGI) (such as epididymitis, proctitis, and perihepatitis), as well as in salpingitis and its sequelae, ectopic pregnancy, sterility, and neonatal eye and chest infections. Treatment aimed at preventing these distressing and costly complications is regularly given to contacts, irrespective of the clinical or laboratory findings. The short and long term benefits of this policy remain undocumented.

Recurrence of NSU in men appears to be an index of latency after treatment. We have no such readily recognizable clinical index in women, and for both sexes culture has so far proved to be of limited value. If the organisms cannot be readily found in the genitourinary tract between and during clinical recurrences, where do they lie dormant? Might it be that they exist (temporarily undetectable by existing methods) in an intracellular form in the surface cells of genital organs, and require repeated in vivo passages before again precipitating signs and symptoms, positive cultures, or reinfection? Might they even be in other organs or systems of the body?

Weston Hurst's laboratory work suggests that at least the latter possibility should be considered. When performing postmortem examinations on his intraperitoneally infected but clinically cured laboratory animals he observed that some had enlarged spleens.[3] On following up this observation he found large viruses in spleens and livers of infected animals, whether or not the organs were enlarged or the animals had suffered relapse after clinical cure by prolonged courses of treatment. The maximum duration of latent infection observed by Weston Hurst in a treated mouse was 277 days.[16] It is clear from his observations that no drug he tested eliminated the infections unless used in overwhelming or lethal doses.[3 13 15 16] Iatrogenic latency was a reality, therefore, to Weston Hurst.

More recent observations

Experiments, clinical observations, and in vitro studies since Weston Hurst's original work suggest that his observations may be germane to the complex problems associated with NSGI.

Jawetz infected mice intracerebrally and intraperitoneally and treated them orally and subcutaneously with tetracycline.[17] His conclusions are worth quoting: "The earlier a drug is administered and the longer high levels are maintained, the greater the likelihood of survival of the animal or even the eradication of the infecting agent. The later drug administration is started, the greater the probability of persistant infection in surviving animals". Finberg found that cerebrospinal fluid (CSF) from some cases of relapsing LGV could infect guinea pigs.[18] Four cases in humans of meningoencephalitis caused by *C trachomatis* have recently been reported.[19 20]

Recent work shows chlamydiae to be highly adapted to the intracellular site.[21] They appear to be sheltered by cells rather than being destroyed by phagocytosis,[22 23] and use the host cells' biochemical constituents for survival, reproduction, and dissemination. Techniques are being devised to ascertain the antimicrobial concentrations attainable intracellularly, and those essential for eradication of the organism.[24] We do not yet know at what stage of chlamydial development, at what concentration, and to what extent each drug acts. All we know is that the ranking of antimicrobial activity in ovo and by inclusion counts in cell culture has been shown to match that of Hurst's animal experiments 20 to 30 years ago.[21]

Intracellular latency, therefore, seems to merit serious consideration. Modern workers confirm that penicillin, folic acid inhibitors, and the tetracyclines cause inclusions to disappear. It is of significance in the present context that these may reappear only after several passages.[21] Such observations are in keeping with the twin phenomena observed by Hurst of latency induced by treatment and a tendency to recur unexpectedly. They are also in keeping with the growing clinical view that these twin phenomena are inseparably associated with NSU. As suggested by Fowler, unapparent and intermittent infectivity is, in

the long term, nearly as common after treatment as before.

Weston Hurst's observations, which are now being substantiated, suggest that the occurence and extent of latency of genitourinary chlamydial infection induced by treatment can no longer be dismissed as a matter of mere conjecture.

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